Turk J Gastroenterol *2016; 27: 284-9*

Demographic characteristics of chronic pancreatitis patients in the era of endosonography: Experience of a single tertiary referral center in Turkey

PANCREAS

Gürhan Şişman[1], Emine Köroğlu[2], Yusuf Erzin[2], İbrahim Hatemi[2], Murat Tuncer[2], Hakan Şentürk[3]

[1]Department of Gastroenterology, Acıbadem University School of Medicine, İstanbul, Turkey
[2]Department of Gastroenterology, İstanbul University Cerrahpaşa School of Medicine, İstanbul, Turkey
[3]Department of Gastroenterology, Bezmialem University School of Medicine, İstanbul, Turkey

Original Article

ABSTRACT

Background/Aims: There are no clinical data available about chronic pancreatitis (CP) on a series of patients of sufficient number in Turkey. In this study, the etiology and clinical features of CP were evaluated in one center, which is a tertiary referral hospital.

Materials and Methods: The files of 168 patients who had been diagnosed with CP in our Medical Faculty between October 2007 and May 2013 were retrospectively analyzed. The etiological factors, symptoms, complications, and treatment methods were analyzed.

Results: The most common etiological factor was alcohol abuse (39%). The average age±SD was 46±15.2 years, and the male:female ratio was 4.2:1 (it was 2.6:1 for other etiologies except alcohol abuse and 15.5:1 in alcoholic CP patients, $p<0.05$). The most frequent complication was diabetes mellitus (44%). The smoking rate was significantly higher in CP patients with pancreatic calcification ($p<0.05$). One-third of the patients received various types of endoscopic treatment. During a mean follow-up period of 42±13 months (range, 6–55), pancreatic cancer was detected in four patients (2.3%).

Conclusion: In majority of the CP patients, the etiology is alcohol abuse in Turkey. The development of diabetes is the most frequent complication of CP, which is independent of the etiology.

Keywords: Chronic pancreatitis, theraphy, endosonography

INTRODUCTION

Chronic pancreatitis (CP) is characterized by inflammation, fibrosis, and irreversible histological damage resulting in the progressive destruction of the exocrine and endocrine functions of the pancreas. The estimated overall incidence and prevalence rate of CP in different geographic locations range between 4 and 7.7/100000 and 13.5 and 41.7/100000, respectively (1-4).

Alcohol abuse is the most common cause of CP in Western countries and is responsible for 60–90% of cases; however, this rate is decreasing (5). Other etiological factors are obstruction, autoimmunity (2–4%), and hereditary and genetic predisposition. Some anatomical variants such as pancreas divisum may also be a causative factor (6). In some Asian countries, such as India, the most frequent forms are tropical pancreatitis and pancreatitis of unknown etiology, which is also called idiopathic CP (ICP) (7,8).

To the best of our knowledge, there are no epidemiological or clinical data about the etiology of CP in Turkey. Therefore, in the present retrospective cohort study, we aimed to report the demographic and clinical characteristics, etiological factors, and outcomes of different treatment modalities in a series of CP patients followed in our center.

MATERIALS and METHODS

Patients

We performed a retrospective chart review of patients who were diagnosed with CP between October 2007 and May 2013. One hundred sixty-eight patients, 136

Address for Correspondence: Emine Köroğlu E-mail: dreminesatir@gmail.com
Received: January 31, 2016 **Accepted:** March 26, 2016

(81%) of them being males, were included. Etiological factors, symptoms, complications, and treatment modalities were obtained from their medical records.

Definitions

The diagnosis of CP was based on a typical medical history and radiological findings of either pancreatic calcification defined by computed tomography (CT) or pancreatic ductal changes reported by the findings of endoscopic retrograde pancreatography or endosonography (EUS). Patients who were diagnosed with the guidance of EUS were assessed according to the Rosemont criteria (9). This classification includes major criteria A (hyperechoic foci with shadowing and calculi of the main pancreatic duct), major criteria B (lobularity with honeycombing), and minor criteria (lobularity without honeycombing, hyperechoic foci without shadowing, cysts, stranding, an irregular contour of the main pancreatic duct, dilated side branches, dilatation of the main pancreatic duct, and hyperechoic margin of the main pancreatic duct). Only patients who were classified as having "consistent CP" according to the Rosemont criteria were included. Those who were classified as having "suggested CP" and "indeterminate CP" were excluded.

The diagnosis of autoimmune CP was based on the criteria proposed by the Japan Pancreas Society (10). Patients with obstructive pancreatitis secondary to the obstruction of the pancreatic duct due to pancreatic cancer were excluded.

Other possible risk factors for the development of CP were evaluated by laboratory tests (hypercalcemia or hypertriglyceridemia) and by radiology [magnetic resonance cholangiopancreatography (MRCP)], including both biliary and pancreatic ducts.

When no clear etiology was evident based on the history, laboratory tests [including genetic tests, such as those for cystic fibrosis transmembrane conductance regulator (CFTR), serine peptidase inhibitor Kazal-type 1 (SPINK1), or serine protease 1 (PRSS1)], or imaging studies, a diagnosis of ICP was made**.** All patients diagnosed with ICP were further investigated for genetic mutations (CFTR, SPINK1, or PRSS1).

Dilatation of the main pancreatic duct was defined as being ≥3.5 mm in the body or ≥1.5 mm in the tail (9). It was accepted as being large-duct disease when the dilatation was ≥7 mm and as small-duct disease when it was ≤3 mm (11). Minimal change CP is defined as a syndrome of pancreatic abdominal pain with no or slight structural changes detected on imaging but with histological inflammation and fibrosis compatible with CP (12).

Methods

The following data were obtained from all patients: presenting symptoms; onset of symptoms; prior and current medications; presence of complications such as diabetes mellitus, pseudocysts, biliary obstruction, splenic vein thrombosis (SVT), duodenal stenosis, and pancreatic cancer; and type of any endoscopic or surgical treatment and its effect on outcomes. The etiology of CP was identified from medical records and classified using the TIGAR-O system (13). Alcohol-related pancreatitis was defined by a daily intake of more than 60 or 80 g of ethanol for women or men, respectively, for more than 5 years.

A diagnosis of pancreatic cancer had to be supported by a histological examination of surgical specimens or a fine-needle biopsy.

The PRSS1 and SPINK1 mutations were investigated by polymerase chain reaction (PCR), and the CFTR mutation was examined by PCR direct sequencing in the ICP group (14,15).

Information on ethics committee approval cannot be provided because this study was retrospective.

Statistical analysis

Data were collected by a statistical software package (SPSS 15.0 for Windows, IBM Corp.; New York, USA) and are expressed as means, with standart deviation (SD) of the mean calculated when appropriate. Categorical variables were compared using Fisher's exact test, and results are expressed as p values.

RESULTS

Etiology and clinical characteristics of patients

One hundred sixty-eight patients (136 males and 32 females, mean age 46±15.2 years) were included. The mean disease duration was 59 (min 12, max 120) months. The median number of attacks of pancreatitis was 4 (0–30). The etiological factors were as follows: alcohol abuse in 66 patients (39%), hyperlipidemia in 14 (8.3%), smoking in 14 (8.3%), and autoimmune pancreatitis in 6 (3.5%). There were two cases of each of the following: hyperparathyroidism, pancreatitis secondary to abdominal trauma, duodenal wall cyst, and CFTR mutation. In the remaining 60 (35.7%) patients, no etiological factor could be identified, so they were accepted as being idiopathic. The three most common mutations (SPINK1, PRSS1, and CFTR) were analyzed in the ICP group, and the CFTR mutation was found to be homozygotic in two patients. The main presenting symptom was abdominal pain (156 patients, 92.8%), and other symptoms were nausea, vomiting, jaundice, and weight loss as presenting complaints. A comparison of CP patients with alcohol abuse and CP patients due to other etiologies is shown in Table 1. There was a significant predominance of males in the alcoholic pancreatitis group (male:female ratio 15.5:1).

When patients were evaluated according to the morphology of the main pancreatic duct, 36 patients (21%) had large-duct disease and 132 (79%) had small-duct or minimal-change disease. A comparison of CP patients with large-duct and small-duct/minimal-change diseases is shown in Table 2.

Table 1. Comparison of alcoholic and non-alcoholic chronic pancreatitis patients by clinical features and complication rates

	Total	Alcoholic	Non-alcoholic	p
Patients	168	66 (39%)	102 (61%)	
Male:female	4.2:1	15.5:1	2.6:1	<0.05
Disease duration (min–max, months)	59 (12–120)	50 (12–108)	52 (12–120)	<0.05
Mean age±SD, years	46±15.2	50±8.9	45.7±17.5	NS
Smoking	72 (42.8%)	42 (63.6%)	30 (29.4%)	<0.05
Complications				
- Diabetes	74 (44%)	34 (51.5%)	40 (39.2%)	NS
- Pseudocyst	58 (34.5%)	20 (30.3%)	38 (37.2%)	NS
- Biliary obstruction	36 (21.4%)	12 (18.1%)	24 (23.5%)	NS
- Splenic vein thrombosis	22 (13.1%)	6 (9%)	16 (15.6%)	NS
- Pancreatic cancer	4 (2.3%)	2 (3%)	2 (1.9%)	NS
- Duodenal stenosis	4 (2.3%)	2 (3%)	2 (1.9%)	NS
Calcification	50 (29.7%)	26 (39.3%)	24 (23.5%)	NS
Endoscopic treatment	64 (38.1%)	26 (39.3%)	38 (37.2%)	NS
Surgical treatment	10 (5.9%)	4 (6%)	6 (5.8%)	NS

NS: not significant

Table 2. Comparison of large-duct and small-duct/minimal-change chronic pancreatitis by clinical features and complication rates

	Large-duct (n=36, 21%)	Small-duct/ minimal-change (n=132, 79%)	p
Mean age±SD, years	49.9±8.2	42.8±12.7	<0.05
Male:Female	32:4	104:28	<0.05
Smoking (n, %)	34 (94%)	38 (28.7%)	<0.05
Etiology (Alcohol, %)	34 (94%)	32 (24.2%)	<0.05
Complications			
- Pseudocyst	18 (50%)	40 (30.3%)	NS
- Diabetes	20 (55.5%)	54 (40.9%)	NS
- Biliary obstruction	10 (28%)	12 (9%)	<0.05
- SVT	10 (28%)	12 (9%)	<0.05
Treatment modality			
- Endoscopic treatment	34 (94%)	30 (22.7%)	<0.05
- Surgical treatment	10 (28%)	0	<0.05

NS: not significant; SVT: splenic vein thrombosis

Complications

Complications were as follows: diabetes in 74 patients (44%), pseudocysts in 58 (34.5%), biliary obstruction in 36 (21.4%), SVT in 22 (13.1%), and duodenal stenosis in 4 (2.3%) patients. In the follow-up period of 42±13 months (range, 6–55 months), four patients with ductal adenocarcinoma were diagnosed, which indicated an annual incidence of cancer of 0.7%. There was no significant difference regarding the rate of complications between the alcoholic CP group and the group with CP due to other causes (p>0.05). There was a significantly higher rate of smoking in the alcoholic CP group than in the other group (p<0.05). The rate of pancreatic calcifications was 29.8% (n=50, 42 males and 8 females) in the whole group. Comparisons between patients with and without calcifications are shown in Table 3. There was a significantly higher rate of smoking in the group of patients with calcifications (p<0.05), but in general, there was no significant difference in the rate of complications between these two groups (p<0.05).

Radiological findings

All patients underwent abdominal ultrasonography. The most common sign on ultrasonography was a dilated main pancreatic duct, which was noted in 96 patients (57%), and pancreatic atrophy was found in 76 patients (45.2%). One hundred ten patients underwent abdominal CT (65%). Dilatation of the main pancreatic duct and pancreatic atrophy were noted in 82 patients (74.5%) and 66 patients (60%) of them, respectively. MRCP was performed in 66 (39%) patients. Dilatation of the main pancreatic duct was seen in 36 (54.5%) of them, and stones in the main pancreatic duct were noted in 14 (21%) of them. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 64 (38%) patients. Dilatation of the main pancreatic duct and stones in the main pancreatic duct were noted in 56 (87.5%) and 20 (31.2%) of these patients, respectively.

One hundred ten (65.4%) patients were diagnosed by EUS, and the most common findings were hyperechoic foci with shadowing and calculi of the main pancreatic duct, which were noted in 40 (36.3%) and 20 (18.1%) of them, respectively.

Endoscopic and surgical management

There was a need for narcotic analgesics for abdominal pain in 35.7% (n=60) of the patients during the follow-up period. Endoscopic therapy was performed in 64 (38.1%) patients. Stenting procedures were as follows: choledochal stenting with plastic stents in 36 patients, stenting of the main pancreatic duct with fenestrated plastic stents in 34, and multiple stenting of the choledochus in four. EUS-assisted celiac block was performed in 24 (14.2%) patients. Linear EUS-assisted cystoenterostomy was performed in 24 (14.2%) patients. In four patients (2.4%) extracorporeal shock wave lithotripsy was performed for stones in the pancreatic duct. Surgery was performed for pain control in 10 (6%) patients in whom medical and/or endoscopic treatment failed. These procedures were as follows: the Whipple procedure in six patients and the Frey procedure in four**.** There were no significant differences in the rates of surgical or endoscopic treatment between the alcoholic and non-alcoholic CP patient groups (Table 1).

DISCUSSION

Chronic pancreatitis is an irreversible inflammatory disease with ongoing destruction of the pancreatic tissue resulting in

attacks of abdominal pain, exocrine and endocrine insufficiency, or both. Alcohol abuse, which is the most common etiological factor of CP in Western countries, was reported in 60–70% of CP patients, but in Asia the majority of CP cases are either related to tropical pancreatitis or idiopathic (7,16-18).

In our series, 39% of CP cases were alcoholic, the rate of ICP was just 35.7%, and nearly all of the alcoholic pancreatitis patients were male (62/66, 94%). The rate of autoimmune pancreatitis was 3.5%, which is similar to that in previous reports (19,20). Compared with westernized countries, the main etiological factor is the same in Turkey. Some studies suggest that genetic mutations may be the underlying causes in those with early-onset ICP (13,14). In Turkey, there have been no reports published on hereditary pancreatitis. In our study, the three most common mutations (SPINK1, PRSS1, and CFTR) were analyzed in the ICP group and the CFTR mutation was found to be homozygotic in two patients. This result may be caused by genetic differences between the Turkish population and those in different geographic areas or the small number of patients in our ICP group. On the other hand, tobacco use is an independent risk factor for the development of CP (21,22). In our study, cigarette smoking was found to be the only risk factor in 14 patients (8.3%). It seems that the etiology of CP in Turkey bears more resemblance with European countries rather than Asian countries.

In our series, the proportion of alcohol-related CP (ACP) was significantly higher among males than females (94% vs. 6%, respectively), and the smoking rate was significantly higher in the ACP group (63.6%), so the characteristics of CP associated with drinking and smoking habits were more common in males (23-25). Other associated factors (i.e., obstruction and auto-immunity) were more commonly observed in females. Alcohol use and smoking may exacerbate the course of CP in males. It was shown in previous studies that alcohol use could result in pancreatic fibrosis by activating stellate cells, and also that smoking is related to premature calcification (25-27). In our series, calcification was found in 29.7% of patients and the rate of smoking was significantly higher than in the group without calcification, which agrees with other studies (23-25).

There was a predominance of males in the group with large-duct disease in our study, which is a finding compatible with the literature (28). Alcohol and tobacco use and complications such as SVT and biliary stenosis were significantly commoner in the large-duct disease group when compared with the small-duct/minimal-change disease group. The higher rates of SVT and biliary stenosis in this group may be due to the increased rate of inflammation and fibrosis secondary to cigarette smoking. Also, the rates of endoscopic and surgical procedures were higher in the large-duct disease group, as was expected.

Endosonography is increasingly used in the diagnosis of CP. A few studies have attempted to evaluate the findings of EUS extensively in CP patients. In this study, it was found that even in patients with an absence of pancreatic calcification, which is the cardinal manifestation of CP, there is still a strong correlation with EUS and histopathological findings (29,30). EUS is a routine procedure in our clinic in patients with a suspected diagnosis of CP. In the case of suspected pancreatic malignancy we perform endoscopic ultrasound-fine needle aspiration (EUS-FNA) to exclude malignancy. The Rosemont classification consists of diagnostic criteria for CP based on the findings of EUS. However, the Rosemont classification for the diagnosis of CP was not found to be superior to standard EUS criteria in some studies (31,32). In our series the majority of patients (n=90, 53.5%) were classified as "consistent with CP" according to this classification. When these patients were classified according to the definition of CP of the North American Pancreatitis Study 2 (NAPS2) (33) group, 70 patients (78%) showed ERCP findings according to the Cambridge classification, CT, or MRCP findings, whereas 16 patients (18%) had histopathological findings obtained by EUS-FNA. Only four patients were diagnosed with the guidance of EUS. The patients who were diagnosed with the guidance of EUS by the Rosemont criteria were also evaluated by the other diagnostic models. These data are shown in Table 4.

Table 3. Comparison of calcific and non-calcific chronic pancreatitis by clinical features and complication rates

	Calcific pancreatitis (n=50, 29.8%)	Non-calcific pancreatitis (n=118, 70.2%)	p
Male: Female	42:8	94:24	NS
Mean age±SD, years	48.8±10.9	46.8±16.2	NS
Disease duration (min–max, months)	50 (12–108)	52 (12–120)	NS
Smoking	32 (64%)	40 (34%)	<0.05
Complications			
- Diabetes	28 (56%)	46 (38%)	NS
- Pseudocyst	16 (32%)	42 (35%)	NS
- Biliary obstruction	12 (24%)	24 (20%)	NS
- Splenic vein thrombosis	2 (4%)	20 (12%)	NS

NS: not significant

Table 4. Patients who were diagnosed in respect of Rosemont classification with EUS guidance evaluated based on other diagnostic models

Method	Male (n, %)	Female (n, %)	Total (n, %)
Histology (EUS-FNA)	12 (19%)	4 (15%)	16 (18%)
Imaging	52 (81%)	22 (85%)	74 (82%)
Total	64	26	90

Imaging includes CT, MRCP, and ERCP
CT: computed tomography; MRCP: magnetic resonance cholangiopancreatography; ERCP: endoscopic retrograde cholangiopancreatography; EUS-FNA: Endoscopic Ultrasound-Fine Needle Aspiration

Original Article

In our series the most common complication was diabetes, which was detected in 44% of patients. The frequency of diabetes in CP is reported to be 40–70%, increasing with disease duration (18,34). Diabetes is generally a late complication of CP and its frequency is correlated with disease duration and also with the severity of parenchymal destruction. In prospective cohort studies the cumulative incidence of diabetes in CP is reported to be 50% and 80%, respectively, 10 and 25 years after the diagnosis of CP. Distal pancreatectomy and the early appearance of pancreatic calcifications are reported to be independent risk factors for the development of diabetes in CP (35). In some studies alcohol consumption is found to be a risk factor for diabetes as well (36). In our study we did not find a difference according to the rate of diabetes in alcoholic and non-alcoholic CP patients. This could be due to short disease duration or the insufficient power of the study. Pseudocysts have been reported to be the second most common complication of CP (7,19,37,38). In the present study pseudocysts were also common (34.5%), but there was no significant difference in the rate of pseudocysts between the alcoholic and non-alcoholic groups.

We cannot estimate the prevalence of exocrine insufficiency because pancreatic function tests were not available in our university, although Western studies have found that exocrine insufficiency is a common complication of CP (14–48%) (36,37).

Pain is usually the cardinal symptom of CP and is difficult to manage. Medical therapy options are limited and are unsuccessful/fail in most cases. In a retrospective case study of a duration of four years, the rate of surgery for pain control in patients who were using opioids was 36.5% (19). In our series, the rate of opioid use was 35.7% (60 patients) and the need for surgery for pain control occurred in 16.6% (10 patients) of opioid users. In fact, one of the distinct findings of our series was the low rate of surgery for pain control (6%). The rate of surgery was reported to be 31% in a United States cohort and 8.2% in an Asian cohort (16,34). The low rate of surgery in our series could be a result of our insufficient cooperation with the surgical team for the management of these patients. Another reason could be the limited number of surgeons specializing in pancreatic surgery in Turkey.

The endoscopic management of CP consists of ERCP performed for the treatment of obstructions or stones in the pancreatic duct, pain control with celiac block assisted by EUS, or treatment of local complications (38). In our study, endoscopic therapy was also performed in 64 (38.1%) of the 168 CP patients, which is a similar rate to other studies (18,34).

Chronic pancreatitis is a well-known risk factor for pancreatic cancer. The incidence of pancreatic cancer during the course of CP has been reported to range from 1.1% to 3% in the Western countries (34,36,39-41). The cumulative risks were reported to be 1.8% and 4%, respectively, 10 and 20 years after diagnosis (36). In our study the overall incidence of pancreatic cancer was 2.3%, which is similar to that in several Western studies (37,41,42).

This study has several strengths and weaknesses. Limitations include the small sample size, cross-sectional cohort, and single-center and retrospective nature of the study. Strengths include the unique features of this study, such as the fact that it is the first example of a nationwide study and the first genetic analysis of ICP patients. Multicenter and prospective studies with larger sample sizes are needed on this topic.

In conclusion, the most common etiology of CP in our series is alcohol consumption (39%), but 35.7% of patients remain idiopathic. The most common complications are diabetes and pseudocyst formation, independent of etiology. Rates of SVT and biliary stenosis were significantly higher in large-duct disease patients. Surgical treatment for CP was infrequently used in our series. In addition, our study shows that ICP patients have a lower incidence of genetic mutations.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.G.; Design - S.G., K.E., E.Y., H.I., T.M.S.H.; Supervision - S.G.; Materials - S.G., K.E., E.Y., H.I., T.M.S.H. .; Data Collection and/or Processing - S.G., K.E., E.Y., H.I., T.M.S.H.; Analysis and/or Interpretation - S.G., K.E., E.Y., H.I., T.M.S.H.; Literature Review - S.G., K.E., E.Y., H.I., T.M.S.H.; Writer - S.G.; Critical Review - S.G., K.E., E.Y., H.I.,T.M.S.H.; Other - S.G., K.E., E.Y., H.I., T.M.S.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Yadav D, Timmons L, Benson JT, Dierkhising RA, Chari ST. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. Am J Gastroenterol 2011; 106: 2192-9. [CrossRef]
2. Levy P, Barthet M, Mollard BR, Amouretti M, Marion-Audibert AM, Dyard F. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. Gastroenterol Clin Biol 2006; 30: 838-44. [CrossRef]
3. Lin Y, Tamakoshi A, Matsuno S, et al. Nationwide epidemiological survey of chronic pancreatitis in Japan. J Gastroenterol 2000; 35: 136-41. [CrossRef]
4. Wang LW, Li ZS, Li SD, Jin ZD, Zou DW, Chen F. Prevalence and clinical features of chronic pancreatitis in China: a retrospective multicenter analysis over 10 years. Pancreas 2009; 38: 248-54. [CrossRef]
5. Cote GA, Yadav D, Slivka A, et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2011; 9: 266-73. [CrossRef]
6. Pezzilli R. Etiology of chronic pancreatitis: has it changed in the last decade? World J Gastroenterol 2009 14; 15: 4737-40. [CrossRef]

7. Garg PK, Tandon RK. Survey on chronic pancreatitis in the Asia-Pacific region. J Gastroenterol Hepatol 2004; 19: 998-1004. [CrossRef]
8. Strate T, Knoefel WT, Yekebas E, Izbicki JR. Chronic pancreatitis: etiology, pathogenesis, diagnosis, and treatment. Int J Colorectal Dis 2003; 18: 97-106.
9. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: The Rosemont classification. Gastrointest Endosc 2009; 69: 1251-61. [CrossRef]
10. Pearson RK, Longnecker DS, Chari ST, et al. Controversies in clinical pancreatology: autoimmune pancreatitis: Does it exist? Pancreas 2003; 27: 1-13. [CrossRef]
11. Yekebas EF, Bogoevski D, Honarpisheh H, et al. Long-term follow-up in small duct chronic pancreatitis: A plea for extended drainage by "V-shaped excision" of the anterior aspect of the pancreas. Ann Surg 2006; 244: 940-6. [CrossRef]
12. Walsh TN, Rode J, Theis BA, Russell RC. Minimal change chronic pancreatitis. Gut 1992; 33: 1566-71. [CrossRef]
13. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001; 120: 682-707. [CrossRef]
14. Lee KH, Ryu JK, Yoon WJ, Lee JK, Kim YT, Yoon YB. Mutation analysis of SPINK1 and CFTR gene in Korean patients with alcoholic chronic pancreatitis. Dig Dis Sci 2005; 50: 1852-6. [CrossRef]
15. Gasiorowska A, Wojnarowska RT, Czupryniak L, et al. The Prevalence of Cationic Trypsinogen (PRSS1) and Serine Protease Inhibitor, Kazal Type 1 (SPINK1) Gene Mutations in Polish Patients with Alcoholic and Idiopathic Chronic Pancreatitis. Dig Dis Sci 2011; 56: 894-901. [CrossRef]
16. Lowenfels AB, Sullivan T, Fiorianti J, Maisonneuve P. The epidemiology and impact of pancreatic diseases in the United States. Curr Gastroenterol Rep 2005; 7: 90-5. [CrossRef]
17. Lankisch PG, Assmus C, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic diseases in Luneburg County. Astudy in a defined German population. Pancreatology 2002; 2: 469-77. [CrossRef]
18. Balakrishnan V, Unnikrishnan AG, Thomas V, et al. Chronic pancreatitis. A prospective nationwide study of 1,086 subjects from India. JOP 2008; 9: 593-600.
19. Frulloni L, Gabbrielli A, Pezzilli R, et al. Chronic pancreatitis: Report from a multicenter Italian survey (PanCroInfAISP) on 893 patients. Digestive and Liver Disease 2009; 41: 311-7. [CrossRef]
20. Ryu JK, Lee JK, Kim YT, et al. Clinical Features of Chronic Pancreatitis in Korea: A Multicenter Nationwide Study. Digestion 2005; 72: 207-11. [CrossRef]
21. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med 2009; 169: 1035-45. [CrossRef]
22. Yadav D, Slivka A, Sherman S, et al. Smoking is underrecognized as a risk factor for chronic pancreatitis. Pancreatology 2010; 10: 713-9. [CrossRef]
23. Cavallini G, Talamini G, Vaona B, et al. Effect of alcohol and smoking on pancreatic lithogenesis in the course of chronic pancreatitis. Pancreas 1994; 9: 42-6. [CrossRef]
24. Maissonneuve P, Lowenfels AB, Mullhaupt B, et al. Cigarette smoking accelerates progression of alcoholic chronic pancreatitis. Gut 2005; 54: 510-4. [CrossRef]
25. Imoto M, DiMagno EP. Cigarette smoking increases the risk of pancreatic calcification in late-onset but not early-onset idiopathic chronic pancreatitis. Pancreas 2000; 21: 115-9. [CrossRef]
26. Apte MV, Phillips PA, Fahmy RG, et al. Does alcohol directly stimulate pancreatic fibrogenesis? Studies with rat pancreatic stellate cells. Gastroenterology 2000; 118: 780-94. [CrossRef]
27. Apte MV, Wilson JS. Stellate cell activation in alcoholic chronic pancreatitis. Pancreas 2003; 27: 316-20. [CrossRef]
28. Gupta V, Toskes PP. Diagnosis and management of chronic pancreatitis. Postgrad Med J 2005; 81: 491-7. [CrossRef]
29. Chong AK, Hawes RH, Hoffman BJ, Adams DB, Lewin DN, Romagnuolo J. Diagnostic performance of EUS for chronic pancreatitis: a comparison with histopathology. Gastrointest Endosc 2007; 65: 808-14. [CrossRef]
30. Varadarajulu S, Eltoum I, Tamhane A, Eloubeidi MA. Histopathologic correlates of noncalcific chronic pancreatitis by EUS: a prospective tissue characterization study. Gastrointest Endosc 2007; 66: 501-9. [CrossRef]
31. Del Pozo D, Poves E, Tabernero S, et al. Conventional versus Rosemont endoscopic ultrasound criteria for chronic pancreatitis: interobserver agreement in same day back-to-back procedures. Pancreatology 2012; 12: 284-7. [CrossRef]
32. Kalmin B, Hoffman B, Hawes R, Romagnuolo J. Conventional versus Rosemont endoscopic ultrasound criteria for chronic pancreatitis: comparing interobserver reliability and intertest agreement.Can J Gastroenterol 2011; 25: 261-4. [CrossRef]
33. Whitcomb DC, Yadav D, Adam S, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). Pancreatology 2008; 8: 520-31. [CrossRef]
34. Choudhuri G, Lakshmi CP, Goel A. Pancreatic diabetes. Trop Gastroenterol 2009; 30: 71-5.
35. Malka D, Hammel P, Sauvanet A, et al. Risk factors for diabetes mellitus in chronic pancreatitis. Gastroenterology 2000; 119: 1324-32. [CrossRef]
36. Thuluvath PJ, Imperio D, Nair S, Cameron JL. Chronic pancreatitis. Long-term pain relief with or without surgery, cancer risk, and mortality. J Clin Gastroenterol 2003; 36: 159-65. [CrossRef]
37. Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMango EP. The different courses of early and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology 1994; 107: 1481-7. [CrossRef]
38. Lee LS, Conwell DL. Update on advanced endoscopic techniques for the pancreas: endoscopic retrograde cholangiopancreatography, drainage and biopsy, and endoscopic ultrasound. Radiol Clin North Am 2012; 50: 547-61. [CrossRef]
39. Lowenfels AB, Maissonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993; 328: 1433-7. [CrossRef]
40. Talamini G, Falconi M, Bassi C, et al. Incidence of cancer in the course of chronic pancreatitis. Am J Gastroenterol 1999; 94: 1253-60. [CrossRef]
41. Amman RW, Knoblauch M, Mohr P, et al. High incidence of extrapancreatic carcinoma in chronic pancreatitis. Scand J Gastroenterol 1980; 15: 395-9. [CrossRef]
42. Lankish PG, Lohr-Happe A, Otto J, Creutzfeldt W. Naturel course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. Digestion 1993; 54: 148-55.